REMARKS

Status of the Claims

Claims 66, 68, 76-85, 117-127, 129, and 130 are pending in the present application. Claim 128 is cancelled with this amendment. Claims 66 and 117 are amended herein to correct grammatical errors.

Rejection Pursuant to 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 66, 68, 76-85, 117-127, 129, and 130 under 35 U.S.C. § 103(a) as being obvious in view of Kveder *et al.* (Farmacevtski Vestnik, 47/SPEC. ISS., pages 163-171, 1996).

As the Office stated, Kveder *et al.* teach a clinical trial with erythropoietin Omega, wherein EPO Omega is produced by the Powell recombinant method *in vitro*. Patients undergoing the clinical trial include those who had required hemodialysis twice or three times per week and who also had hemoglobin levels below 85 grams per liter or below 90 grams per liter when they had been dependent on frequent transfusions. Kveder *et al.* show that it is possible to achieve a correction of anemia within a relatively short period of time in patients with chronic kidney failure who were being treated with dialysis. As the Office further pointed out, Kveder *et al.* do **not teach** the administration of EPO omega to subjects who are non-responsive or adversely affected when treated with a therapeutic amount of Epoetin Alfa or Beta. However, the Office alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Kveder *et al.* to use EPO omega to treat patients who are non-responsive or adversely affected with Epoetin Alfa or Beta because EPO omega was efficacious and well tolerated. Applicants respectfully disagree.

Claim 66 relates to a method of treating an anemic condition in a subject by administering to the subject a therapeutic amount of a recombinant Epoetin Omega, wherein the amount of recombinant erythropoietin administered is selected to provide a therapeutic benefit within a

treatment period, and wherein the subject is non responsive when treated with a therapeutic amount of Epoetin Alfa or Beta. Similarly, claim 117 relates to a method of treating an anemic condition with Epoetin Omega, wherein the subject is adversely affected when treated with Epoetin Alfa or Beta. Claims 68 and 76-85 depend from claim 66, and claims 118-127 and 129-130 depend from claim 117.

Epoetin Alfa and Beta are glycoproteins with average molecular weight of about 41 kD, which are produced from erythropoietin genomic DNA and cDNA, respectively in Chinese hamster ovary (CHO) cells. Epoetin Beta is almost identical to Epoetin Alfa, but contains minor isoforms in addition to the major isoforms observed with Epoetin Alfa.

One of the significant side effects experienced with administration of either Epoetin Alfa or Epoetin Beta is a routine increase in blood pressure, which can lead to hypertension on initial dosing, and continued complications during maintenance periods. Other adverse effects include seizures, headaches, thrombosis, flu-like symptoms, and increased pain at the site of the injection. Certain subjects also experience adverse effects such as chronic pain or fatigue, or are non-responsive to treatment. These side effects, and particularly increase in blood pressure, mean that a number of patients have to stop Epoetin Alfa and/or Beta therapy due to adverse reactions or non-responsiveness. Kveder *et al.* describe such side effects reported for EPO Alfa and/or Beta, as well as favorable effects of EPO Alfa and/or Beta administration including reduced itching, improved cognitive function and quality of life (see sections 3.1 and 3.2).

Erythropoietin Omega is a glycoprotein with molecular weight of about 39 kD. It is produced in baby hamster kidney (BHK) cells from an Apa I human genomic EPO fragment. At the time the invention was made, one skilled in the art would have expected that a glycoprotein made from the same EPO gene as EPO Alfa and Beta, having very similar size (about 39 kD for EPO omega vs. about 41 kD for EPO Alfa and EPO Beta), and being made in a similar mammalian culture system would have similar properties to EPO Alfa and EPO Beta. Accordingly, one would have expected that EPO Omega would have a similar, if not the same, function and side effects as Epoetins Alfa and Beta. In fact, Kveder *et al.* report that 17% of the

patients experienced increased blood pressure, 1 in 30 had to suspend treatment due to allergic reaction, and 1 in 30 reported pain during administration. These results are consistent with those reported in sections 3.1 and 3.2 for administration of EPO Alfa and/or Beta.

However, as described in the specification, on page 5:

> Provided herein is the discovery that Epoetin Omega is **surprisingly different** from epoetins Alfa and Beta in the type and severity of adverse side effects caused by Epoetin Alfa or Beta, which makes it particularly useful for treatment of certain disease states such as oncology/cancer especially in conjunction with chemo or radiation therapy. (Emphasis added.)

Based on the structural similarities of Epoetins Alfa, Beta, and Omega, one skilled in the art would have expected at the time the invention was made that a subject, who is non-responsive when treated with Epoetin Alfa and/or Beta, would also be non-responsive when treated with Epoetin Omega. In a similar fashion, a skilled artisan would have expected that a subject who is adversely affected by the treatment with Epoetin Alfa and/or Beta would also be adversely affected by Epoetin Omega.

Accordingly, based on the knowledge available at the time the invention was made, a skilled artisan would **not** have expected that EPO omega would exhibit significantly more potency, higher serum concentration over clearance time, and lower doses in both initial treatment and maintenance compared to EPO Alfa and Beta. More importantly, a skilled artisan could not have predicted that the increase in blood pressure, which is one of the major adverse effects associated with EPO Alfa and Beta would be absent from the treatment with EPO Omega. Furthermore, one would not have expected that EPO omega would be effective in subjects non-responsive to or adversely affected by treatment with other Epoetins.

Accordingly, the differences in function and side effects exhibited by EPO omega in comparison to Epoetins Alfa and Beta would not have been expected by a skilled artisan. Thus, it would <u>not</u> have been obvious to treat patients who are non-responsive or adversely affected by

Epoetin Alfa and/or Beta with EPO omega as described by Kveder *et al.* On the contrary, at the time of the invention, the non-responsiveness and side effects experienced by a number of patients who were treated with Epoetin Alfa or Beta would have **led** one skilled in the art **away** from trying to treat such patients with EPO Omega because they would have been expected to react similarily regardless of the type of EPO administered.

In view of the foregoing, Applicants submit that claims 66 and 117 are non-obvious over Kveder *et al.* Furthermore, claims 68 and 76-85, and claims 118-127 and 129-130, which depend from claims 66 and 117, respectively, are non-obvious over Kveder *et al.* for the same reasons as the independent claims.

CONCLUSION

In view of the above, Applicants respectfully request favorable reconsideration and allowance of the pending claims.

The Commissioner is hereby authorized to charge any deficiency or overpayment of the required fee to Deposit Account No. 19-1345.

Respectfully submitted,

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